NOV 23 2005

This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21!

See attached form for additional information.

Interagency Report Control No.:

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 14-R-0144
CUSTOMER NUMBER: 1799

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

Charles River Laboratories Inc
251 Ballardvale St
Wilmington, MA 01887

Telephone: (508) -658-6000

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Atached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (**Attach additional sheets if necessarv or use APHIS Form 7023A**)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasc such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs	191	1627	1106	10	2743
5. Cats					
6. Guinea Pigs	28	5367	1523	1	6891
7. Hamsters	4	1412	50		1462
8. Rabbits	200	6000	578	33	6611
9. Non-human Primates	2446	1772	1514		3286
10. Sheep			154		154
11. Pigs	66	493	1684	14	2191
12. Other Farm Animals					
Cattle			19		19
Goats			49		49
13. Other Animals					
Cotton Rats	92	40	175		215
Gerbils		17			17
Degu	162	27			27

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquillizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary inc brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)

(B)(6) (B)(7)(c)

DATE SIGNED
11/23/200

(AUG 91)

Charles River Laboratories
Customer #: 1799
USDA Research Registration #14-R-0144

Attachment #1

Site #	Address
002	Charles River Laboratories Research Models & Services (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)
003	Charles River Laboratories Preclinical Services (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)
005	Charles River Laboratories Preclinical Services - (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)
013	Charles River Laboratories Preclinical Services (b)(2) hig (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)
014	Charles River Laboratories Preclinical Services (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)
016	Charles River Laboratories Preclinical Services (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)
017	Charles River Laboratories Preclinical Services - (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)
018	Charles River Laboratories (b)(2) high, (b)(7)(F) (b)(2) high, (b)(7)(F)

019 Charles River Laboratories Interventional & Surgical Services (b)(2) high, (b)(7)(F)
(b)(2) high, (b)(7)(F)

020 Charles River Laboratories Consulting & Staffing Services (b)(2) high, (b)(7)(F)
(b)(2) high, (b)(7)(F)

021 Charles River Laboratories Research Models & Services – (b)(2) high, (b)(7)(F)
(b)(2) high, (b)(7)(F)

Preface:

Animals placed in Column "E" in this report were utilized in Preclinical Services Facilities (listed above) belonging to Charles River Laboratories . These animals were enrolled in studies undertaken for product registration purposes based on regulatory guidelines of the FDA 21 CFR 312.23 for pharmacology and toxicology studies and the Red Book. Guidance for study design and conduct also conformed with recommendations by the International Conference on Harmonization Guidelines. This guidance includes Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on non-clinical safety studies for the conduct of human clinical trial for pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997.

Depending upon the nature of the compound, certain other regulations and guidelines promulgated by the FDA, EPA, TSCA, FIFRA and the OECD also apply and are listed in the Applicable Guidelines/Regulations section below.

Animals could be placed in Category "E" both prospectively and retrospectively. Retrospective diagnosis of pain or distress was made by the Attending Veterinarian in conjunction with the Study Director. In order to insure that under reporting did not occur, the magnitude and duration of clinical signs were considered in making the diagnosis of pain or distress as was the length of time between the development of clinical signs and actions such as discontinuation of compound administration, administration of therapeutic measures that may or may not have included the use of analgesics or euthanasia. Animals that were moribund or had any clinical signs of sufficient magnitude to warrant early termination from the study (moribund euthanasia) were included only if there was, in the opinion of the Attending Veterinarian, a delay in conducting euthanasia in order to acquire additional data or if there was a failure in treatment regimens to resolve the condition. Animals showing any clinical of acute toxicity, even though they were mild or were not specifically related to pain or distress, were included if the animal was maintained on study following the development of such signs for more than a reasonable period of time for the signs to resolve (usually less than 24 hours) without the initiation of treatment to relieve the signs or to address the possible presence of pain or if the animal was not euthanized at that time. Any animals placed in Category "E" prospectively were assigned at the time of IACUC protocol review and were generally not re-categorized.

REVIEW OF CATETORY "E" STUDIES

The following studies have been listed in Category "E" based upon the guidelines stated in the preface at the beginning of this report. Studies classified into Category "E" were conducted at Charles River Laboratories Preclinical Services located in Horsham, PA (Site # 014) and Redfield, AR (Site # 016) facilities. The study designs that resulted in certain animals being placed retrospectively into Category "E" were required by federal regulations and guidelines listed in the applicable regulations/guidelines section below. For the purpose of this report studies have been given a unique number that corresponds to the actual study number. For reasons of confidentiality, actual study numbers are not presented but are available to the USDA for on-site inspection or report follow-up. Category "E" explanations/details are listed separately for each study at each of the two sites.

CHARLES RIVER LABS PRECLINICAL SERVICES- ARKANSAS (Redfield, AK - 016)

Study: #1
Animals: 2 dogs (one in high-dose group and one in control group)
Type of Study: 28-day repeated dose toxicity
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003

- Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997

***See Applicable Regulations Section**

Diagnosis: Distress
Signs contributing to the diagnosis: Decreased activity, ataxia, prostration, increased salivation, frothy vomitus, discoloration of skin, labored breathing.
Disposition: Clinical signs were transient lasting only several hours. Animals returned to normal and continued on study until terminal euthanasia at end of study.

Study: #4
Animals: 3 dogs (two in high/low-dose group, one in high-dose group)
Type of Study: 14-day repeated dose
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003

- Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997

***See Applicable Regulations Section**

Diagnosis: Distress
Signs contributing to the diagnosis: Decreased activity, increased heart rate, non-arousable, red material in mouth and on body (not blood) considered to be part of dosed compound, cold to the touch, labored breathing.
Disposition: Dose level was significantly lowered after clinical signs were (Day 5) seen. One dog was found dead after above signs first appeared (Day 5). Two dogs were found in moribund condition and both were euthanized (1 and 2 days following lowering of dose). The duration of the premonitory signs resulted in classification.

Study: #5
Animals: 1 dog (in mid-high dose group)
Type of Study:
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003

- Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997

***See Applicable Regulations Section**

Diagnosis: Distress
Signs contributing to the diagnosis: One dog found dead after having an impaired limb function for 2 days.
Disposition: The dog was found dead.

Study: #6
Animals: 1 dog (in mid-dose group)
Type of Study: Intravenous injection (escalating dose)
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

***See Applicable Regulations Section**

Diagnosis: Distress
Signs contributing to the diagnosis: Ataxia (Day 1) abnormal stool, labored breathing, decreased activity (Day 2). A decision was made to euthanize on Day 3.
Disposition: The dog was found dead on Day 3 of study before euthanasia occurred. The duration of the premonitory signs resulted in classification.

Study: #7
Animals: 1 rabbit
Type of Study: Multiple dose toxicity study
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003

- Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997

***See Applicable Regulations Section**

Diagnosis: Pain
Signs contributing to the diagnosis: Fractured right forelimb 12 hours after being observed as normal
Disposition: Animal was euthanized immediately upon discovery of injury.

Study: #10
Animals: 4 rabbits
Type of Study: Maintenance and training protocol for testing facility
Guidelines/Regulations: None
Diagnosis: Distress
Signs contributing to the diagnosis: Three animals were found dead immediately following gavage training. One animal found dead post-op on Day 4 after supportive treatment had been given for 1 day for reduced food intake. Necropsy revealed pneumonia. Classification is due to the nature of and the suspected duration of this condition.
Disposition: Animals found dead.

Study: #11
Animals: 1 rabbit (low-dose group)
Type of Study: Intravenous (Jugular Access Ports) Toxicity Study in Pregnant Rabbits
Guidelines/Regulations: None
Diagnosis: Distress
Signs contributing to the diagnosis: Lethargy
Disposition: Decreased feed consumption for 3 days, lethargy for 1 day and necropsy findings of possible intestinal torsion. No clinical manifestations of pain were noted. The duration of the premonitory signs, combined with necropsy findings resulted in classification.

Study: #12
Animals: 5 rabbits (mid-high dose group)
Type of Study: Oral (Gavage Stomach Tube) Developmental toxicity Study in Pregnant Rabbits
Guidelines/Regulations:

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97) 186/Final).
- Organisation for Economic Co-operation and Development Guidelines for the Testing of Chemicals, Method 414: Teratogenicity [C(83) 44 (Final)].1983
- U.S. Environmental Protection Agency (1998). Health Effects Test Guidelines; Prenatal Developmental Toxicity Study. Office of Prevention, Pesticides and Toxic Substances (OPPTS) 870.3700, August, 1998.
- U.S. Environmental Protection Agency. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); Good Laboratory Practice Standards; Final Rule. 40 CFR part 160.

Diagnosis: Distress
Signs contributing to the diagnosis: Seizures
Disposition: 5 animals found dead as a result of an accidental injury during dosage administration, as determined by necropsy

Study: #13
Animals: 2 rabbits (one mid-dose group and one high-dose group)
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study
Guidelines/Regulations:

- U.S. Food and Drug Administration (1994). International Conference on Harmonisation; guideline on detection of toxicity to reproduction for medicinal products. *Federal Register,* September 22, 1994, Vol. 59, No. 183

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

- Japanese Ministry of Health, Labor and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs,* MHW Ordinance Number 21, March 26, 1997.

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

Diagnosis: Distress/Pain
Signs contributing to the diagnosis: One animal was discovered with fracture limb from possible accidental injury during transport. One animal observed on second day of dosage as having weight loss, dilated pupils and splayed limbs. This animal was found moribund the following day and died before euthanasia could be performed.
Disposition: The first animal was euthanized immediately upon discovery of injury. The second animal died before euthanasia could be performed

Study: #14
Animals: 1 rabbit (low-dose group)
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study
Guidelines/Regulations:

- U.S. Food and Drug Administration (1994). International Conference on Harmonisation; guideline on detection of toxicity to reproduction for medicinal products. *Federal Register,* September 22, 1994, Vol. 59, No. 183

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

- Japanese Ministry of Health, Labor and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs,* MHW Ordinance Number 21, March 26, 1997.

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

Diagnosis: Distress
Signs contributing to the diagnosis: Un-groomed coat, slight to moderate salivation and hyper reactivity. The necropsy finding of localized infection of pharyngeal tissues, presumably as a result of accidental injury to the respiratory tract during dosage administration
Disposition: The duration of the premonitory signs and necropsy findings resulted in classification. Animal was euthanized.

Study: #15
Animals: 1 rabbit (high-dose group)
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study
Guidelines/Regulations:

- U.S. Food and Drug Administration (1994). International Conference on Harmonisation; guideline on detection of toxicity to reproduction for medicinal products. *Federal Register,* September 22, 1994, Vol. 59, No. 183

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

- Japanese Ministry of Health, Labor and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs,* MHW Ordinance Number 21, March 26, 1997.

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

Diagnosis: Distress
Signs contributing to the diagnosis: Weight loss, soft feces, decreased motor activity.
Disposition: Animal was found dead. Death presumably as a result of an accidental injury to respiratory tract during dosage administration the day prior to being found dead, as determined at necropsy.

Study: #16
Animals: 1 rabbit (high-dose group)
Type of Study: Subcutaneous Dosage Range Toxicity Study in Non-pregnant Rabbits
Guidelines/Regulations:

U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

Diagnosis: Distress
Signs contributing to the diagnosis: Stopped eating, decreased motor activity, impaired righting reflex and shallow respirations post-dosing.
Disposition: Animal died before euthanasia could be performed

Study: #17
Animals: 5 rabbits
Type of Study: Oral (Gavage) Developmental Toxicity Study
Guidelines/Regulations:

- U.S. Food and Drug Administration (1994). International Conference on Harmonisation; guideline on detection of toxicity to reproduction for medicinal products. *Federal Register,* September 22, 1994, Vol. 59, No. 183

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

- Japanese Ministry of Health, Labor and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs,* MHW Ordinance Number 21, March 26, 1997.

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

Diagnosis: Distress
Signs contributing to the diagnosis: No clinical signs were noted.
Disposition: Animals died immediately following accidental injury during dosing procedure (gavage).

Study: #18A
Animals: 1 rabbit (in low-dose group) (Part A of study)
Type of Study: Oral (Stomach Tube) Dosage Range Developmental Toxicity Study in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration (1994). International Conference on Harmonisation; guideline on detection of toxicity to reproduction for medicinal products. *Federal Register,* September 22, 1994, Vol. 59, No. 183

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

- Japanese Ministry of Health, Labor and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs,* MHW Ordinance Number 21, March 26, 1997.

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

Diagnosis: Distress
Signs contributing to the diagnosis:
One animal was observed bleeding from the mouth from which it recovered. This animal was found dead later that same day. Necropsy revealed a tongue laceration and blood clot formation in the tissues of the neck.
Disposition: Animal was found dead.

Study: #18B
Animals: 11 rabbits
Type of Study: Toxicokinetic Study
Dosage levels selected were 100 times lower than the dosage levels used in Part A.
Guidelines/Regulations:

- U.S. Food and Drug Administration (1994). International Conference on Harmonisation; guideline on detection of toxicity to reproduction for medicinal products. *Federal Register,* September 22, 1994, Vol. 59, No. 183

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

- Japanese Ministry of Health, Labor and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs,* MHW Ordinance Number 21, March 26, 1997.

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

Diagnosis: Distress
Signs contributing to the diagnosis: Blood loss.
Disposition: Prior to the decision of the study director to euthanize any animal showing evidence of blood loss due to compound related effect.
5 animals were found dead
5 animals were euthanized because they were found moribund
1 animal was found dead apparently caused by accidental injury during dosage administration

Study: #19
Animals: 1 rabbit (in high-dose group)
Type of Study: Oral Gavage Developmental Toxicity Study
Guidelines/Regulations:

- U.S. Food and Drug Administration (1994). International Conference on Harmonisation; guideline on detection of toxicity to reproduction for medicinal products. *Federal Register,* September 22, 1994, Vol. 59, No. 183

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58

- Japanese Ministry of Health, Labor and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs,* MHW Ordinance Number 21, March 26, 1997.

- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

Diagnosis: Pain
Signs contributing to the diagnosis: Fractured limb
Disposition: Animal was euthanized approximately 20 hours after injury likely occurred.

Study: #8
Animals: 1 dog (high-dose group)
Type of Study: 14-day repeated dose toxicity study
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003

- Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997

***See Applicable Regulations Section**

Diagnosis: Distress
Signs contributing to the diagnosis: Ataxia, prostration, soft stool, vomitus, red skin discoloration, labored breathing and increased salivation.
Disposition: The dog was found dead at the 4-hour post-dose observation period.

Study: #9
Animals: 1 pig
Type of Study: Dermal toxicity
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003

- Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997

***See Applicable Regulations Section**

Diagnosis: Distress
Signs contributing to the diagnosis: Sensitivity to touch, erythema, edema.
Disposition: The pig was treated with analgesics for dermal pain but did not completely respond to therapy. The animal was continued on study even though signs persisted at a reduced level and some pain upon handling was still present. The animal was euthanized at the end of the study.

Study: #2
Animals: 13 pigs (in low-mid to high-dose groups)
Type of Study: Dermal toxicity study
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003

- Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997

***See Applicable Regulations Section**

Diagnosis: Pain
Signs contributing to the diagnosis: Elevated dermal irritation scores, red discharge, sensitivity to touch, vocalization, fissuring, scabbing, desquamation and/or ulceration.
Disposition: Dosing suspended for 5 days and treatment regimen with analgesics was started. One animal euthanized in moribund condition after 7th day of treatment regimen. All animals (except the euthanized moribund animal) continued on study through scheduled euthanasia. The duration of the premonitory signs resulted in classification.

Study: #3
Animals: 2 dogs
Type of Study: Dose escalation/range finding
Guidelines/Regulations:

- Although not required by federal regulations, this study was conducted as a precursor to a 14-day repeated dose and the results were considered necessary to conduct the GLP study.

Diagnosis: Distress
Signs contributing to the diagnosis: One dog developed labored breathing, prostration, decreased activity, vomitus, excessive salivation and soft stool.
Disposition: One dog had resolution of clinical signs within 12 hours of dosing but was removed from the study. One dog was euthanized in moribund condition. The duration of the premonitory signs resulted in classification.

Study: #20
Animals: 1 guinea pig
Type of Study: Topical Photoallergy Screening Test
Guidelines/Regulations:

- U.S. Food and Drug Administration (2000). *Guidance for Industry – Photosafety Testing (Draft).* Pharmacology Toxicology Coordinating Committee, Center for Drug Evaluation and Research (CDER), January 3, 2000, pp. 1-22.

- Organisation for Economic Co-operation and Development (1987), *Guidelines for Testing of Chemicals.* Section 4, No. 402: Acute Dermal Toxicity, pp. 1-7.

Diagnosis: Distress
Signs contributing to the diagnosis: The animal was weak, reluctant to move, had bilateral ptosis and trembled when handled, not eating and dehydrated.
Disposition: Euthanasia was recommended immediately upon discovery of clinical signs of distress. However, the animal died prior to euthanasia.

IACUC-APPROVED EXCEPTIONS TO REGULATIONS AND STANDARDS

Charles River Laboratories Preclinical Services, MA
and Interventional and Surgical Services, MA

The IACUC and the Attending Veterinarian must approve exemptions from non-human primate social housing and dog exercise activities. Monitoring of these animals during the period that they are exempted is performed by the technical staff with oversight from the Veterinary Staff to ensure that the animals do not exhibit stereotypic behaviors that are detrimental to their overall health and well-being. The following exceptions to standards/regulations were approved by the IACUC during this reporting period.

Species: Macaca sp. (Cynomolgus and/or Rhesus)
Number: 344
All animals were on metabolism and pharmacokinetics studies. Pair housing, environmental enrichment devices inside the cage and/or dietary supplimentation (no fruit peels or peanut shells) were withheld after dose administration for 1-14 days during sample collection due to study requirements. External stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided. Environmental enrichment devices were allowed outside the cage.

Species: Macaca sp. (Cynomolgus)
Number: 36
All animals were on toxicology, pharmacology or surgical studies. Pair housing, environmental enrichment devices inside the cage and/or dietary supplimentation (no fruit peels or peanut shells) were withheld after dose administration for up to 60 days during sample collection due to study requirements. External stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided. Environmental enrichment devices were allowed outside the cage.

Species: Macaca sp. (Cynomolgus)
Number: 8
All animals were on a toxicology study. Pair housing, environmental enrichment devices inside the cage and/or dietary supplementation (no fruit peels or peanut shells) were withheld after dose administration for up to 158 days during sample collection due to study requirements. External stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided. Environmental enrichment devices were allowed outside the cage.

Species: Canis familiaris (Dog)
Number: 207
All animals were on metabolism and pharmacokinetics studies. Pair housing and/or exercise were withheld after dose administration for 1-14 days during sample collection. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. The animals were observed daily for signs of distress from lack of exercise during the exemption period. No animals were noted to be adversely affected during this period.

Species: Canis familiaris (Dog)
Number: 188
All animals were on toxicology or pharmacology studies. Pair housing and/or exercise were exempted after dose administration for 6-50 days during sample collection. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. The animals were observed daily for signs of distress from lack of exercise during the exemption period. No animals were noted to be adversely affected during this period.

Species: Canis familiaris (Dog)
Number: 194
All animals were on surgical studies. Pair housing and/or exercise were exempted after surgery for up to 30 days to facilitate recovery. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. The animals were observed daily for signs of distress from lack of exercise during the exemption period. No animals were noted to be adversely affected during this period.

Applicable Regulations/Guidelines

The following are applicable guidelines and regulations covering the conduct of studies at all Charles River Laboratory Preclinical Services Facilities (listed above).

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003.
- PART VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, No. 227, Nov 25, 1997
- EPA Health Effects Test Guidelines OPPTS 870.3050, 28-Day Oral Toxicity in Rodents, July 2000
- EPA Health Effects Test Guidelines OPPTS 870.3150, 90-Day Oral Toxicity in Non-Rodents, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.3100, 90-Day Oral Toxicity in Rodents, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.4100, Chronic Toxicity, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.3500, Preliminary Developmental Toxicology Screen, March 1994
- EPA Health Effects Test Guidelines OPPTS 870.3600, Inhalational Developmental toxicity Study March 1994
- EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study, August 1995
- EPA Health Effects Test Guidelines OPPTS 870.3800, Reproduction and Fertility Effects, August 1995
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 90-day Oral Toxicity Studies in Non-Rodents, 409, September 1998
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 90-day Oral Toxicity Studies in Rodents, 408, September 1998
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 28-day Oral Toxicity Studies in Rodents, 407, July 1995